ClearView Healthcare Partners

Biotechnology Innovation Organization

Landscape of Innovation

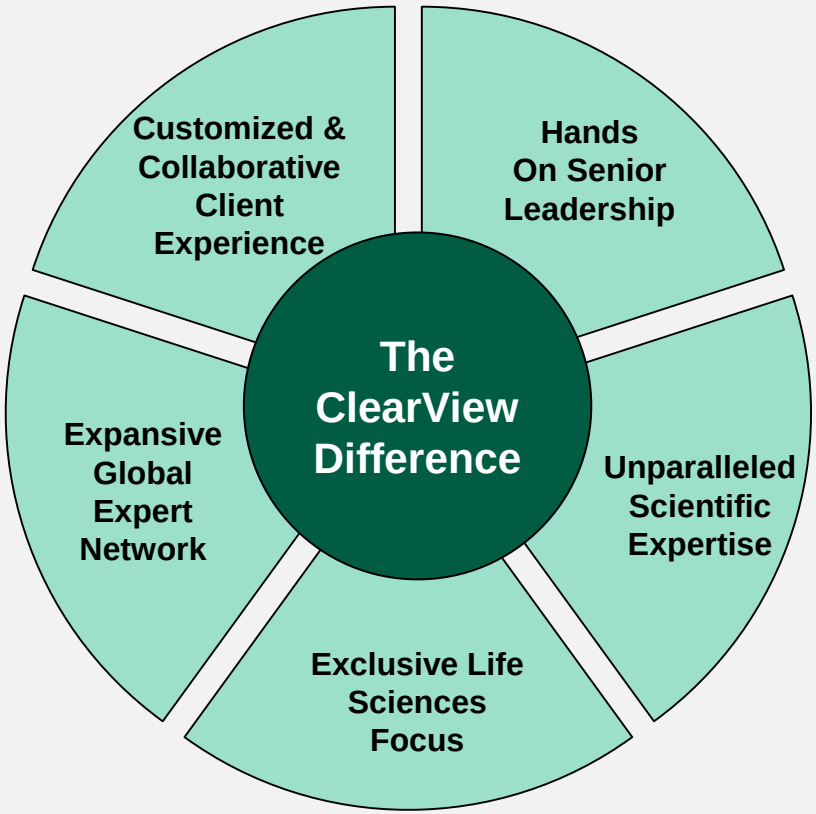
Drivers of Value for Innovators

June 3, 2019

ClearView Healthcare Partners

We provide the best available strategic life sciences consulting support on issues that require both strategic insight and deep content expertise

The ClearView Difference



About Us

3 **Offices** (Boston, New York, San Francisco) serving a global client base

19 Members of **leadership team** dedicated to world class execution

200 **Consultants** on professional staff relentlessly focused on client value

2000+ Successfully executed **client engagements**

Our ability to deliver actionable recommendations is derived from the depth of our experience reflecting real world clinical and commercial issues.

Strong Strategic Perspective

300+ years of combined life science consulting experience within the leadership team alone

Hands-on Senior Leadership

1 – 2 dedicated partners and strong supporting team committed to project needs and success

Expansive Global Expert Network

40+ countries where we conduct primary research

5 team members exclusively dedicated to managing our expert network

Extensive Domain Knowledge

>430 projects conducted in 2018, with experience across all key therapeutic areas and commercially meaningful indications

Deep Scientific Expertise

100% of the ClearView consulting team has a life sciences background

We support clients on a broad range of strategic engagements, often involving innovation-related opportunities to enhance shareholder value.

- Corporate Growth Strategy
- Market or Therapeutic-area Entry Strategy
- Company P&L
- Business-unit Assessment
- Market Development Strategy
- Pitch Support
- Workshop Facilitation
- Biosimilars Strategy
- Buy-side and Sell-side Company Due Diligence
- Acquisition Identification and Screening
- Licensing and Acquisition Support

- MOA Mapping
- Portfolio Management
- Mechanism and Pipeline Prioritization
- Indication Triage
- Adjacency Assessment
- Franchise Business Case
- Benchmarking Assessment
- Franchise Growth Strategy
- Disease or Franchise Forecast
- Patient Services Strategy
- Companion Diagnostics Strategy
- Therapeutic Needs Assessment

- Opportunity Assessment
- Competitive Intelligence and Monitoring
- Indication Prioritization
- KOL, Influencer, and CoE Mapping
- Go-to-market Strategy
- Launch Readiness
- Asset Screening and Due Diligence
- LCM Identification and Prioritization
- Product Playbooks
- Brand Positioning and Messaging Strategy
- Clinical Trial Strategy
- Asset Forecasting / P&L

- Launch Pricing Strategy
- U.S./Global Access Landscape
- Global Launch Strategy/Sequencing
- Disruptive Trend Analysis
- Buying Process Analysis
- Early Stage Pricing Strategy
- Innovative Contracting Strategy
- Lifecycle Pricing Management
- HTA and Payer Evidence Planning
- Value Proposition Development
- Value Driver Analysis
- HEOR Endpoint Testing
- Rapid P&MA Opportunity Evaluation
- Revenue Forecasting

Key Questions for Discussion – Trends in Innovation

1 Which innovative therapeutic classes and modalities attracted VC funding in 2018?

2 What therapeutic classes stand out as notable areas for discussion?

Our analysis looked at the portfolio strategies across 30 companies with the largest venture raises in 2018 to assess the landscape of innovation.

Top Venture Raises of 2018

Top 15 U.S. Venture Raises

samumed
braeburn
Allogene THERAPEUTICS
moderna messenger therapeutics
PRECISION BIOSCIENCES
ALECTOR THERAPIES TO REMEMBER
Constellation PHARMACEUTICALS
TCR² THERAPEUTICS
ATRECA
generation bio
Rakuten Medical
RELAY THERAPEUTICS
Kaleido
gossamerbio
celularity

Top 15 Ex-U.S. Venture Raises

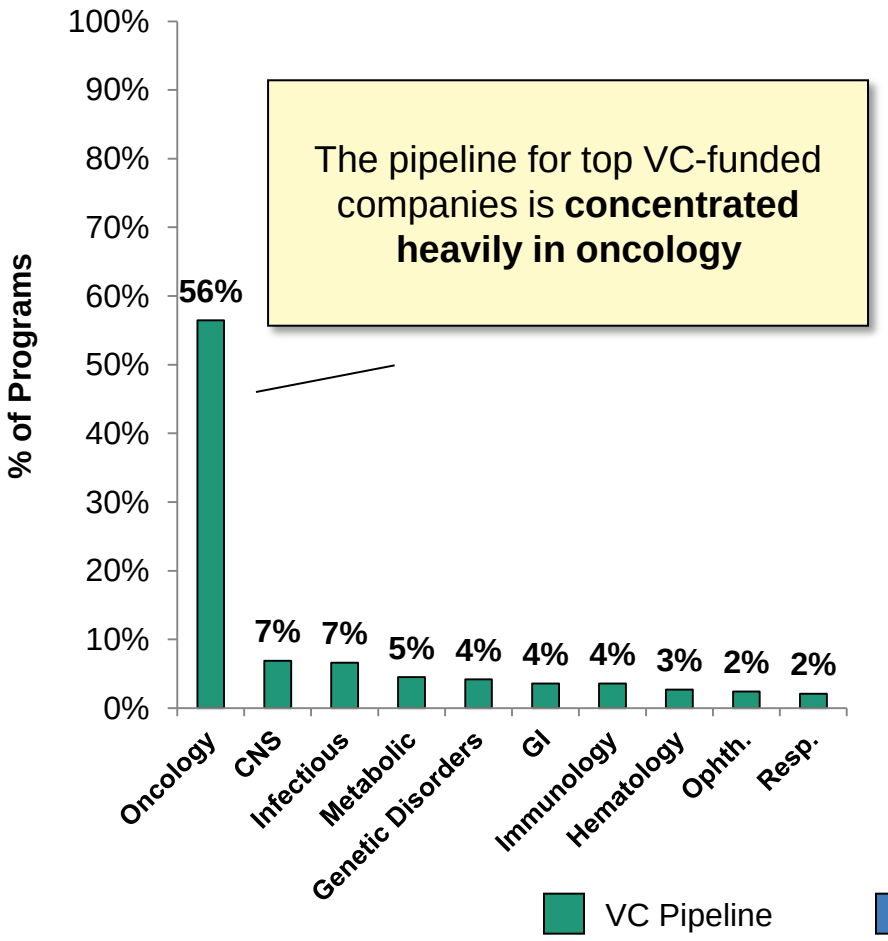
Galecto
TOT BIOPHARM
康宁杰瑞 ALPHAMAB
BenevolentAI
Orchard therapeutics
基石药业 CSTONE PHARMACEUTICALS
药明巨诺 JW Therapeutics
天境生物 I-MAB BIOPHARMA
BIONTECH
Brii Biosciences Breakthrough innovation & insight
INNOCARE
FREELINE THERAPEUTICS
亞盛醫藥 Ascentage Pharma
HUA MEDICINE
Innovent

Pipeline analyses were conducted for the companies above to identify promising, innovative therapeutic classes that have attracted venture capital funding over the last year

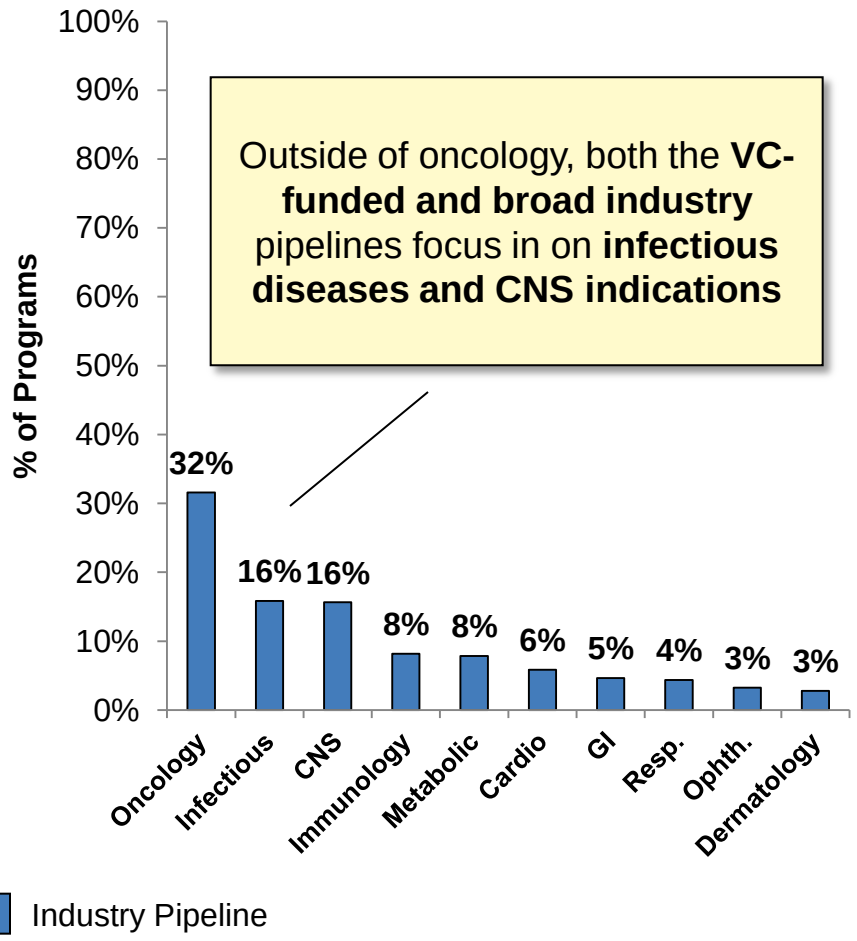
Source: ClearView Analysis.

The top VC-funded company pipeline is relatively similar in distribution to the industry pipeline, though a disproportionate focus on oncology exists.

Top TAs in VC Development Pipeline



Top TAs in Industry Drug Development[1]



Source: Global Data; ClearView Analysis. [1] Reported as a proportion of total drugs being explored in the Top 10; includes programs designated as discovery, preclinical, P1, P2, P3, and Pre-registration (N=27,661); does not account for drugs being explored in multiple therapeutic areas.

Venture capital funding in the past year reflects an increasing trend of large raises directed towards the development of platform technologies.

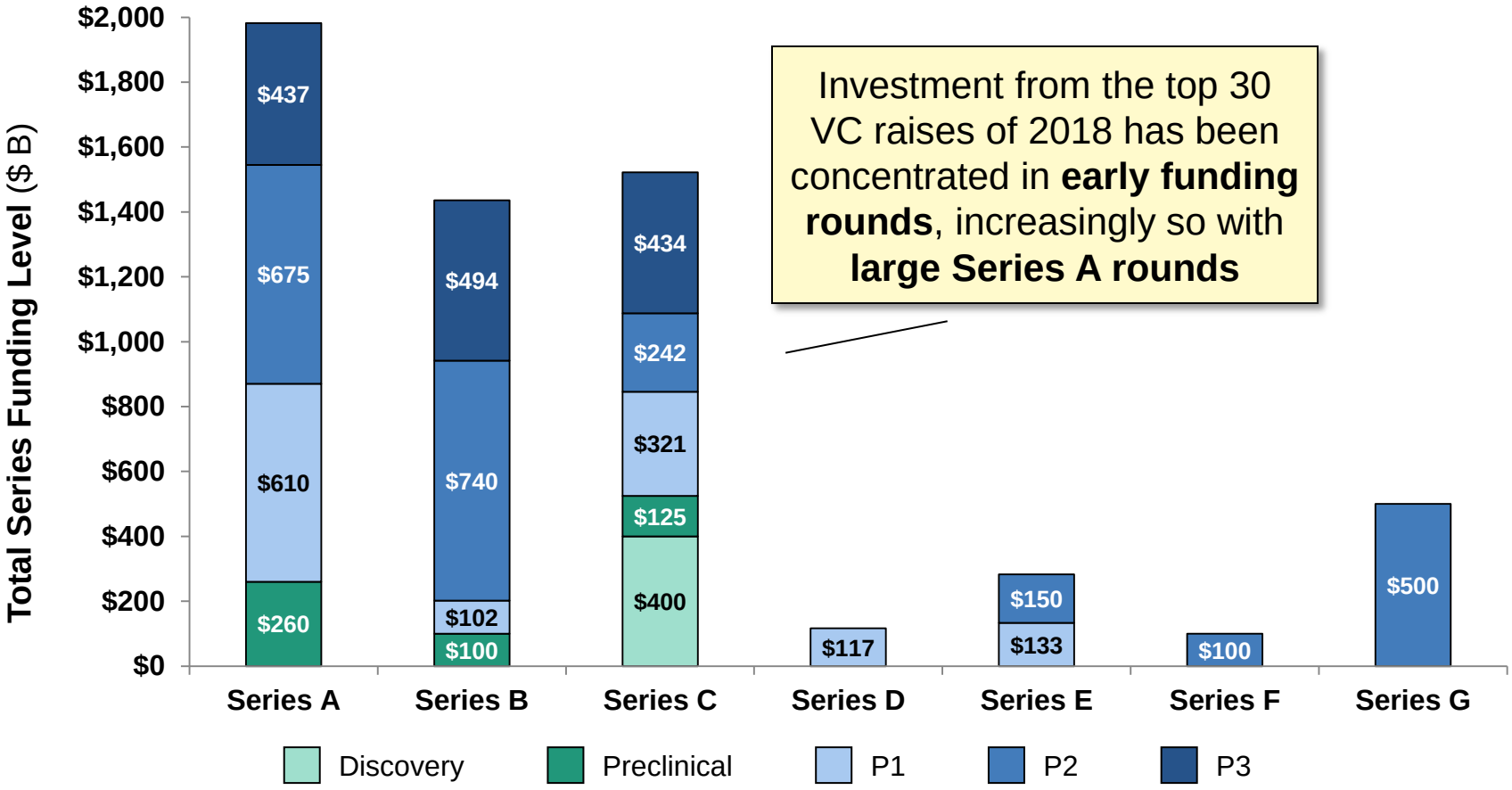
Therapeutic Classes in the VC Development Pipeline

Therapeutic Class	% of Companies[1]	% of Pipeline Assets
Nucleic Acid Technologies *(Including Cell and Gene Therapy)*	~30%	~34%
Antibody Technology	~18%	~24%
Small Molecules	~34%	~20%
Recombinant & Fusion Proteins	~3%	~4%
Polysaccharides	~3%	~2%
Other Therapeutic Classes[2]	~12%	~16%

Source: Global Data; ClearView Analysis. [1] Top 30 VC companies classified based on where majority of pipeline lies (e.g., in small molecules, antibody technologies); [2] Includes assets with undisclosed mechanisms of action.

This focus on disruptive technologies is reflected by the significant growth in early investments in nascent technologies.

Funding Rounds by Companies' Latest Development Stage[1]



Source: Global Data; ClearView Analysis. [1] Denotes latest development stage in global, U.S., or EU trials.

To create value, innovators must differentiate their technologies across diverse applications while ensuring operational focus and fiscal discipline.

For innovator companies, how do you balance pursuit of a breadth of potential applications against focused advancement of a single lead program?

How does the path to value creation differ for innovator companies focused on a platform technology versus a clearly defined lead asset?

For investors, what are the greatest value-driving activities that innovator companies can pursue? What value inflection points do you consider critical to providing funding?

How have current markets affected your collective approaches to (seeking) investment? How does the flow of global capital, and the rise of global innovators, affect your approach?

Source: ClearView Analysis.

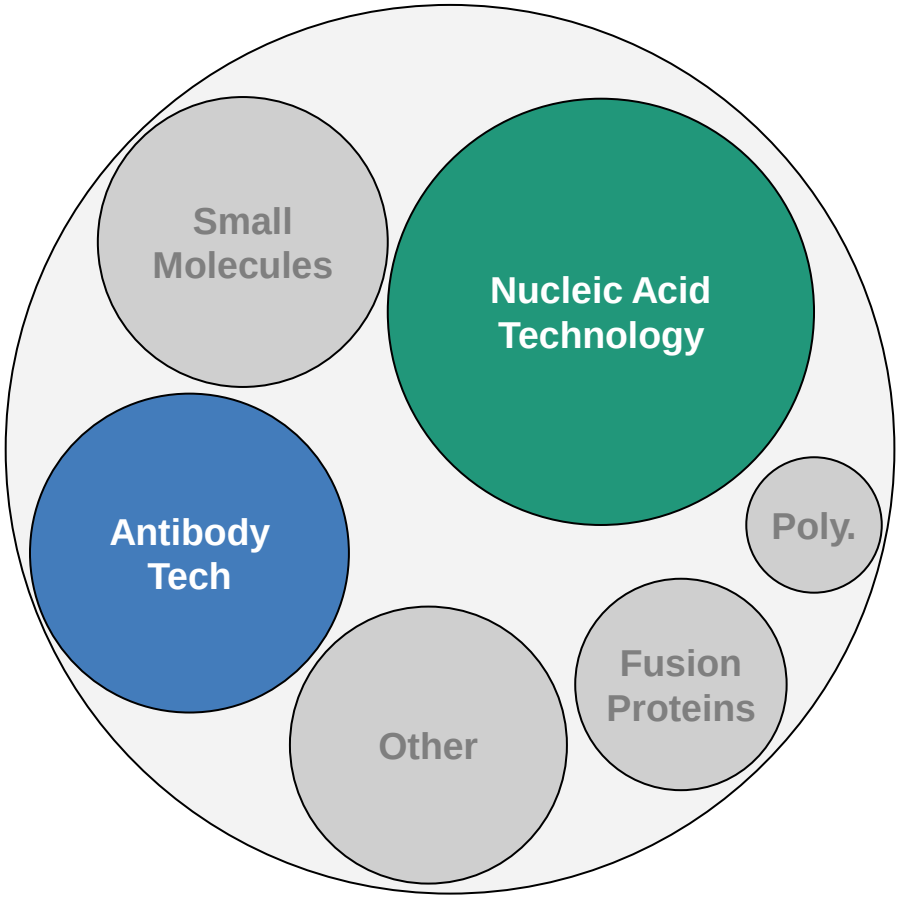
Trends by Therapeutic Class

1 What have been the key trends in pharmaceutical development and innovation in 2018?

2 What therapeutic classes stand out as notable areas for discussion?

Companies with significant venture capital funding in the past year possess pipelines that focus heavily on nucleic acid technology and novel antibodies.

VC Development Pipeline



Therapeutic Classes of Interest

Nucleic Acid Technologies
(Including Cell and Gene Therapy)

- **Ex vivo**
- **In vivo**
- **Non-DNA**

Various nucleic acid modalities are being explored to address indications spanning a broad array of TAs

Antibody Technologies

- **Monoclonal Ab**
- **ADC**
- **Bispecific**

Bispecific antibodies comprise ~10% of the broader antibody technology pipeline

Source: Global Data; ClearView Analysis. ADC: Antibody Drug Conjugate.

Trends by Therapeutic Class – Nucleic Acid Technology

1 What have been the key trends in pharmaceutical development and innovation in 2018?

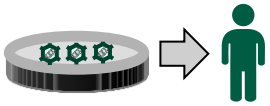
2 What therapeutic classes stand out as notable areas for discussion?

Nucleic Acid Technologies

Novel Antibody Technologies

Nucleic acid technologies encompass a variety of therapeutic modalities, spanning ex vivo and in vivo gene therapies, as well as non-DNA therapies.

Nucleic Acid Technologies



Adoptive Cell Therapy

Ex vivo Stem Cell Therapy

1 Ex Vivo Gene Therapies

- Ex vivo therapies are produced by transfecting host cells in vitro and re-introducing modified cells
- Novel editing techniques (e.g., ZFN, CRISPR) are increasingly being used in addition to viral vectors

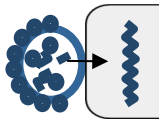
Example Agents

KYMRIAH (tisagenlecleucel) Suspension for IV infusion

Strimvelis

NOVARTIS

Orchard therapeutics



Extra-chromosomal Gene Therapy

In Vivo Genome Editing

2 In Vivo Gene Therapies

- In vivo approaches include extra-chromosomal therapies employing viral vectors (e.g., AAV) and therapies that perform genome editing within the body

Example Agents

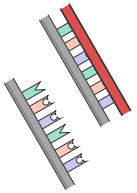
zolgensma®

LUXTURNA™ voretigene neparvovec-rzyl for subretinal injection

NOVARTIS

avexis

Spark THERAPEUTICS



Antisense Oligonucleotides (ASO)

RNAi

mRNA Therapy

3 Non-DNA Nucleotide Therapies

- RNA-based therapies are used to modify translation in various ways
- ASOs / RNAi inhibit gene expression, while mRNA therapy uses translation of delivered mRNA to confer therapeutic benefit

Example Agents

onpattro® (patisiran) lipid complex injection 10 mg/5 mL

SPINRAZA® (nusinersen) injection 12 mg/5 mL

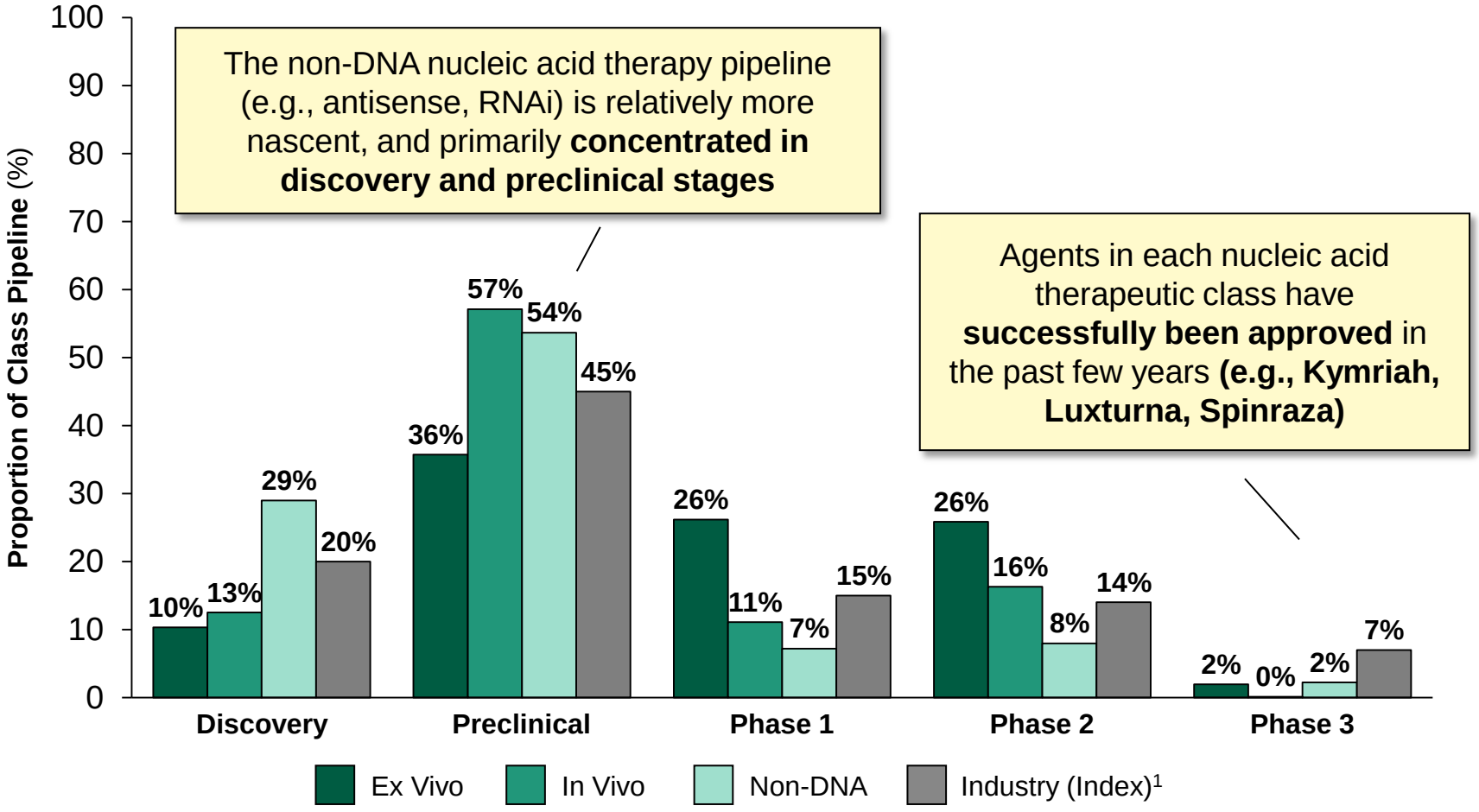
Alnylam PHARMACEUTICALS

Biogen

Source: ClearView Analysis. ASO: Antisense Oligonucleotide. CAR-NK: Chimeric Antigen Receptor – Natural Killer Cell; CAR-T: Chimeric Antigen Receptor – T cell.

Within the nucleic acid therapy space, ex vivo therapies are relatively more mature as a class, with a greater proportion of clinical stage programs.

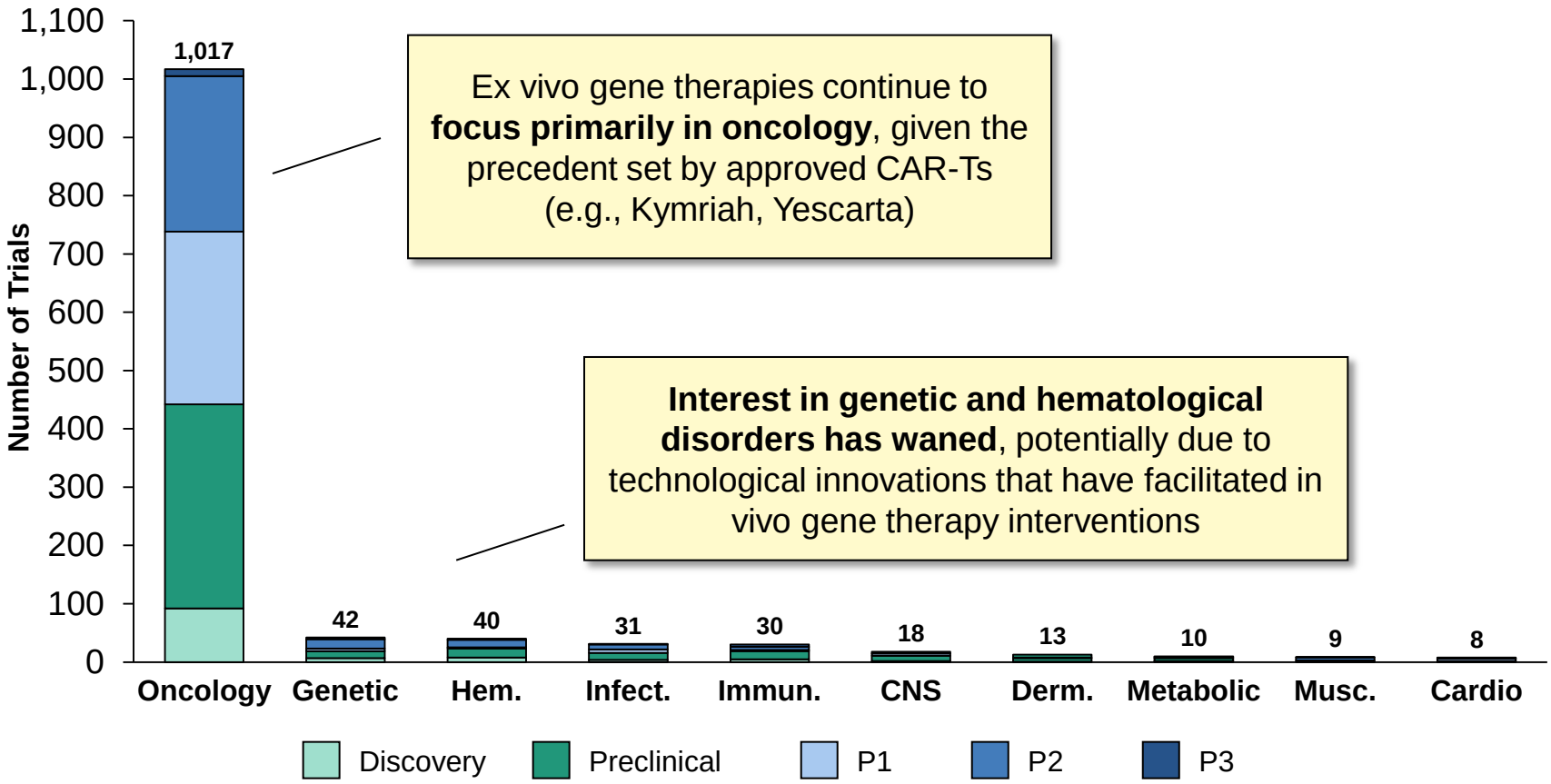
Nucleic Acid Therapy Pipeline Distribution by Development Phase



Source: Global Data; ClearView Analysis. [1] Distribution of industry-wide pipeline by development phase. Note: Includes non-global programs captured by Global Data (e.g., development solely in China).

The ex vivo gene therapy pipeline is concentrated heavily in oncology, where approved CAR-Ts have validated the therapeutic class.

Top 10 TAs in the Ex Vivo Gene Therapy Pipeline



Ex vivo gene therapies continue to **focus primarily in oncology**, given the precedent set by approved CAR-Ts (e.g., Kymriah, Yescarta)

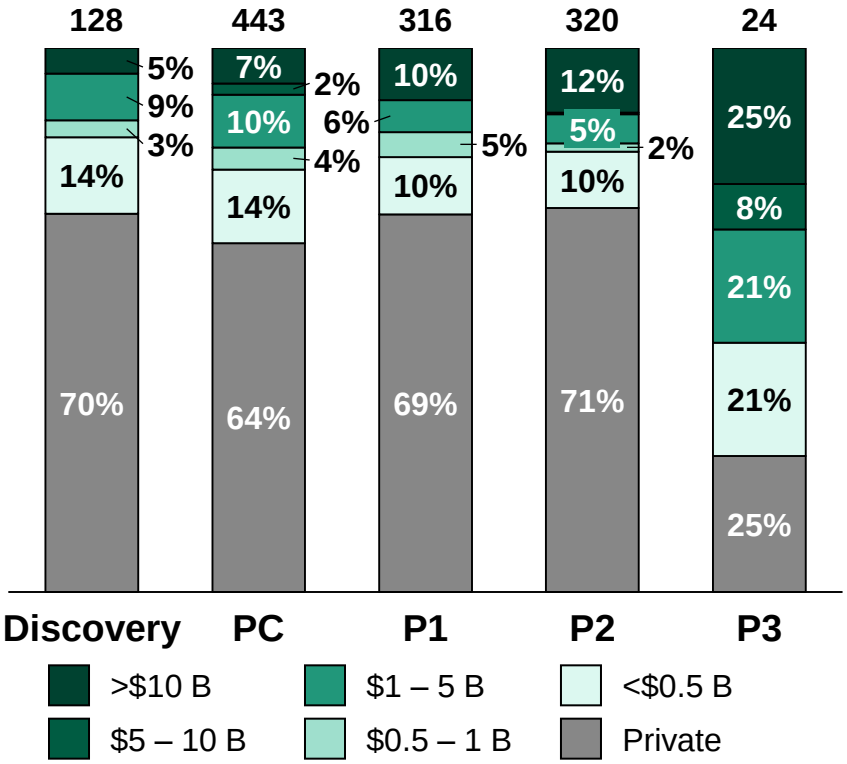
Interest in genetic and hematological disorders has waned, potentially due to technological innovations that have facilitated in vivo gene therapy interventions

Source: Global Data; ClearView Analysis. Note: Includes non-global programs captured by Global Data (e.g., development solely in China).

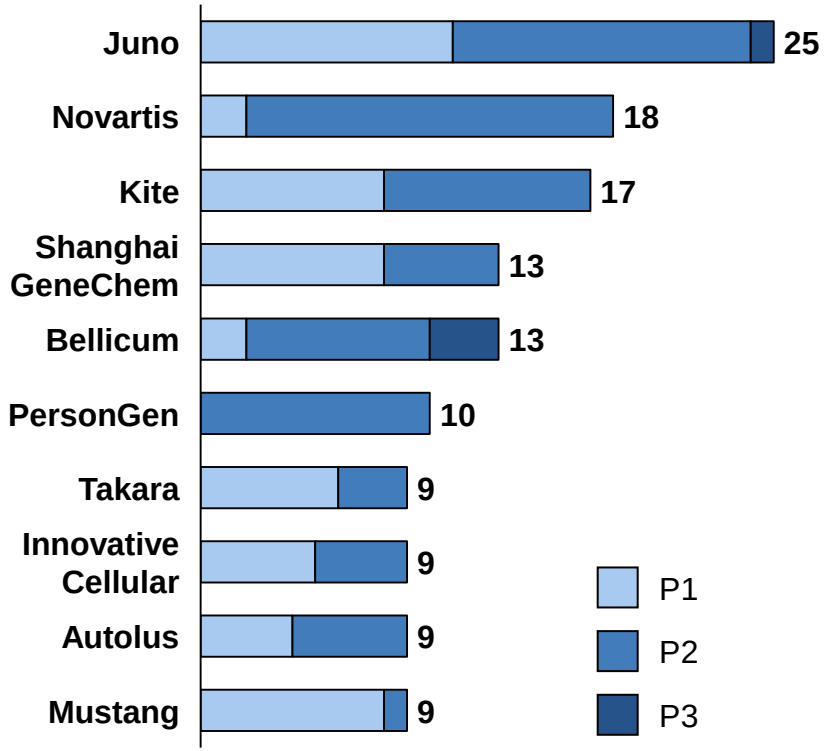
Late-stage ex vivo therapy programs are being pursued by public companies of all sizes, while early programs are driven by small, private biotechs.

Top Players in the Ex Vivo Gene Therapy Pipeline

Distribution of Ex Vivo R&D Projects by Market Cap (2019)



Key Players (P1 – 3 Programs, 2019)

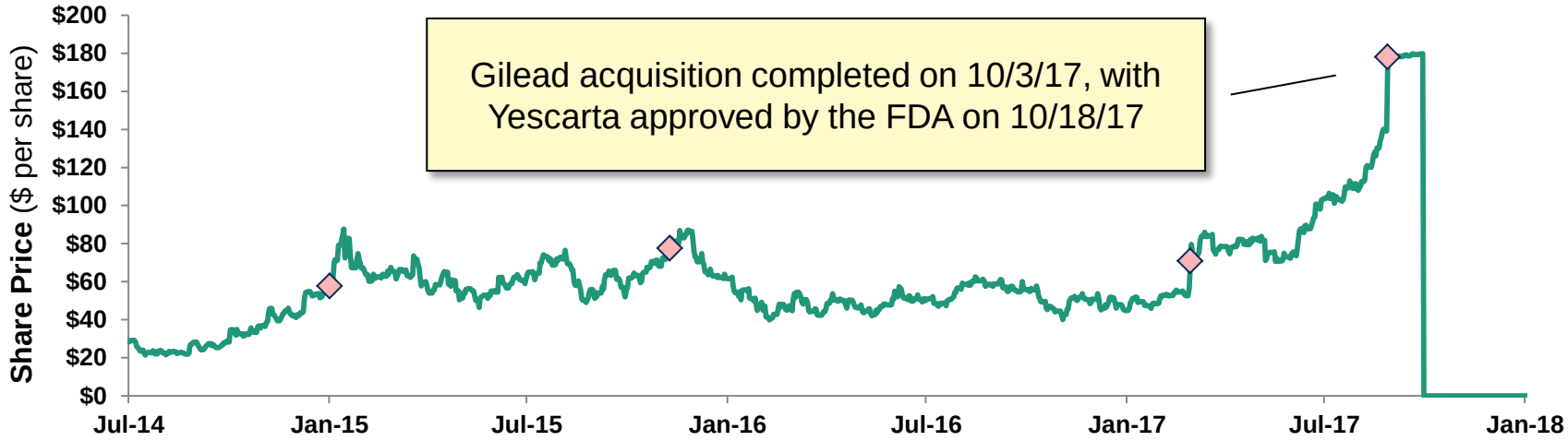


Source: Global Data; Evaluate Pharma; ClearView Analysis. [1] Juno and Kite have been acquired by larger biopharmaceutical companies (Celgene and Gilead, respectively). Note: Includes non-global programs captured by Global Data (e.g., development solely in China).

Companies like Kite Pharma have driven tremendous value by advancing their platform and demonstrating differentiated clinical benefit.

Ex Vivo Gene Therapy Development Case Study

Company: Kite Pharma **Agent:** YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion **Indication:** *R/R Large B-cell Lymphoma*

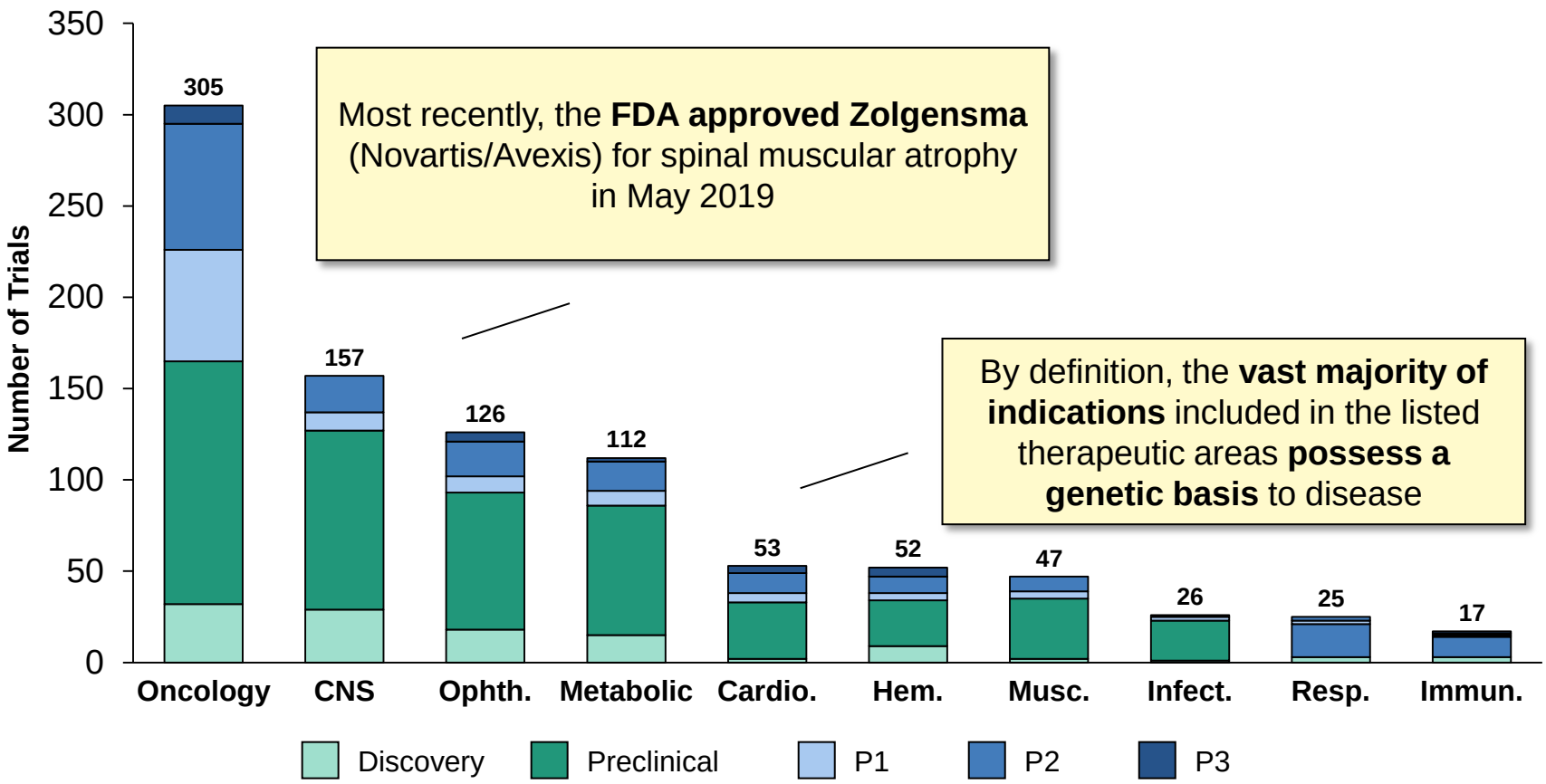


1	**1/1/15**	**2**	**11/9/15**	**3**	**2/28/17**	**4**	**8/28/17**
P1/2 trial in NHL patients initiated (ZUMA-1)		*P2 trial initiated in R/R Mantle Cell Lymphoma (ZUMA-2)*		*Positive data from primary analysis of ZUMA-1 announced*		*Gilead announces acquisition of Kite for $11.9 B*	

Source: Global Data; Evaluate Pharma; Yahoo Finance; ClearView Analysis. NHL: Non-Hodgkin's Lymphoma; R/R: Relapsed/Refractory.

The in vivo pipeline focus is spread more evenly across TAs compared to the ex vivo pipeline, with heavy investment in CNS and ophthalmology.

Top 10 TAs in the In Vivo Gene Therapy Pipeline

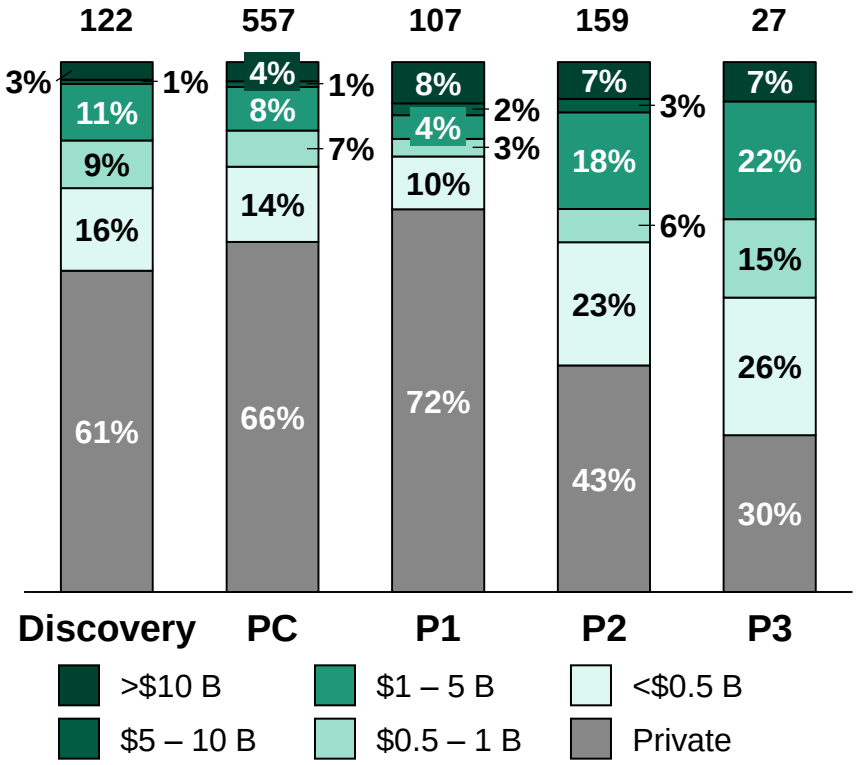


Source: Global Data; ClearView Analysis. Note: Includes non-global programs captured by Global Data (e.g., development solely in China).

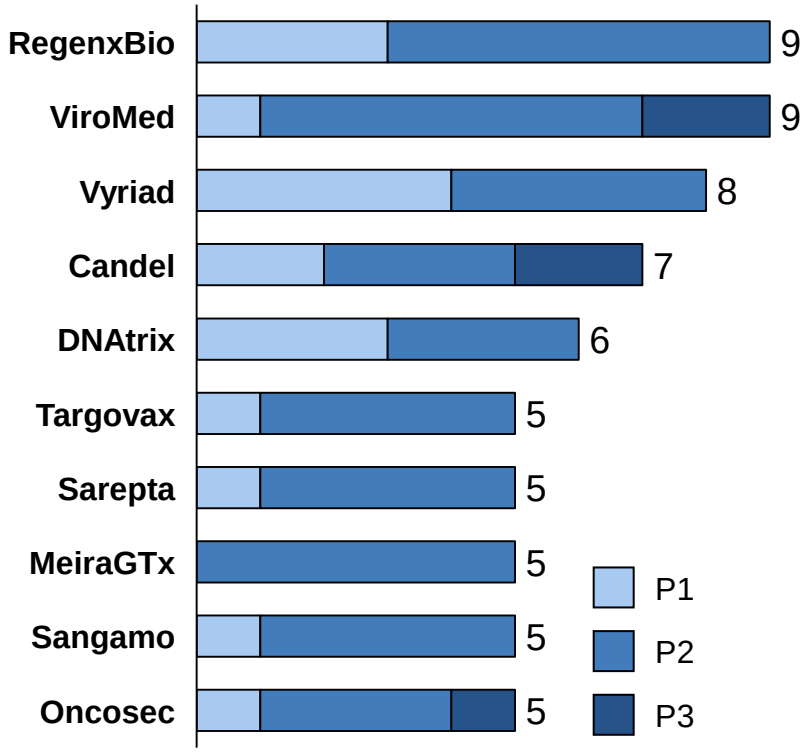
Early research is dominated by private biotechs while larger pharma companies typically become involved in later stages of development.

Top Players in the In Vivo Gene Therapy Pipeline

Distribution of In Vivo R&D Projects by Market Cap (2019)



Key Players (P1 – 3 Programs, 2019)

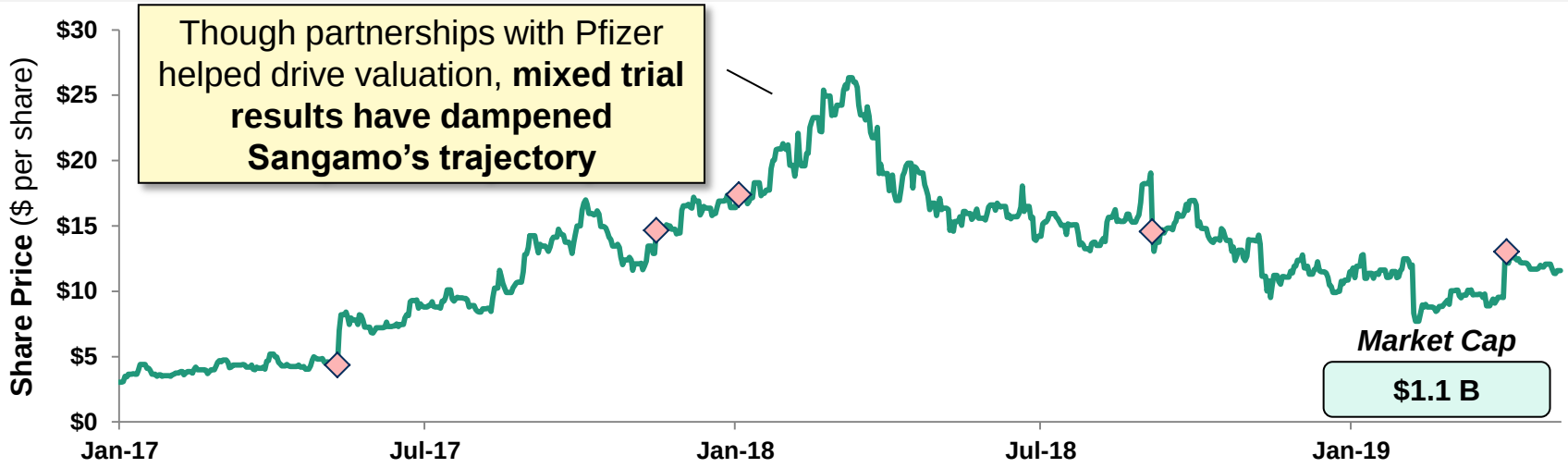


Source: Global Data; Evaluate Pharma; ClearView Analysis. PC: Preclinical. Note: Includes non-global programs captured by Global Data (e.g., development solely in China).

Sangamo generated meaningful value in part through partnerships that validated its strategy, though mixed trial results have impacted that value.

In Vivo Gene Therapy Development Case Study

Company: Sangamo THERAPEUTICS **Key Agent(s):** *SB-525 (Hemophilia A); SB-318 (MPS I); SB-913 (MPS II)*

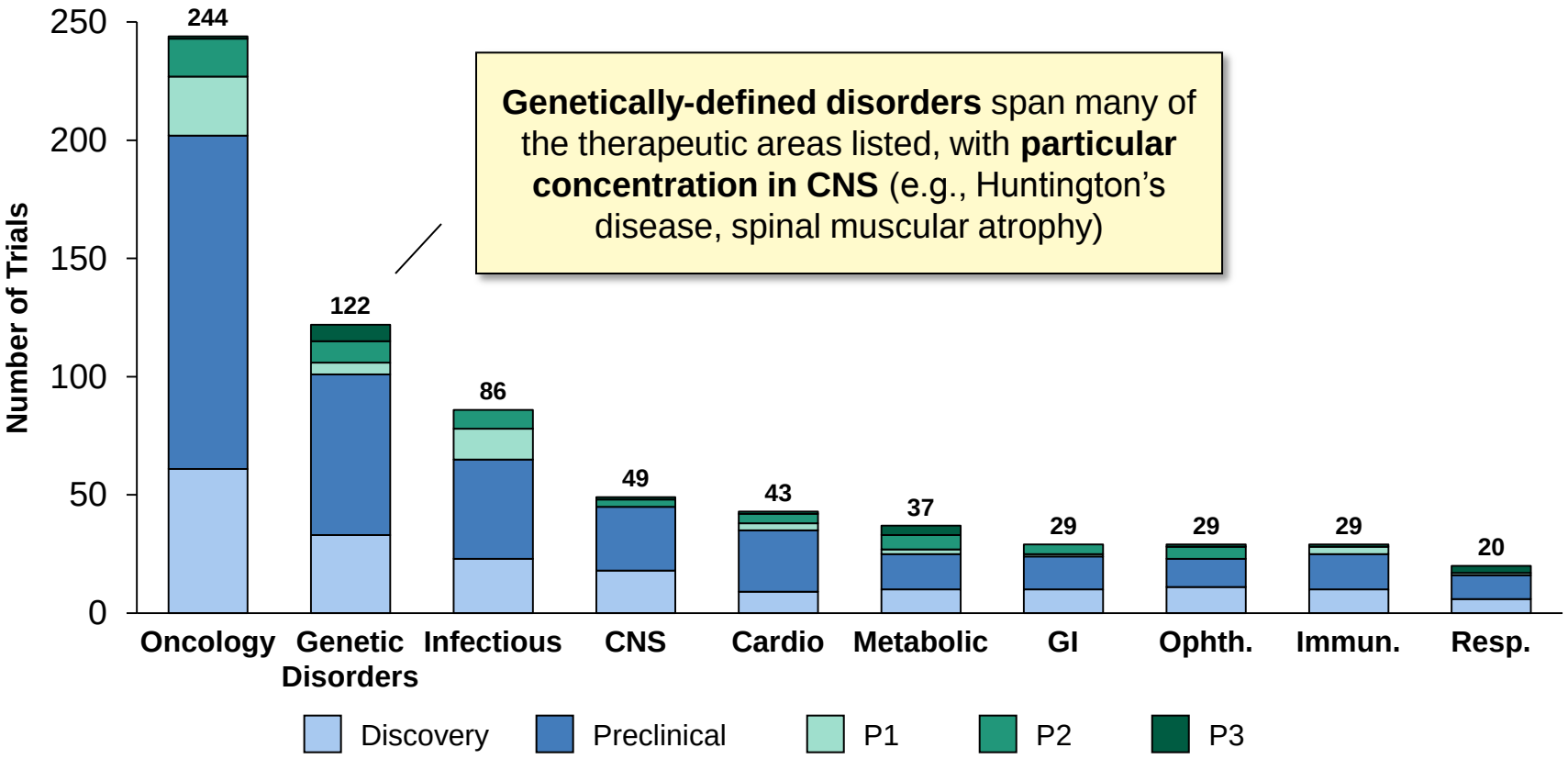


1	**5/10/17**	**2**	**11/15/17**	**3**	**1/3/18**	**4**	**9/5/18**	**5**	**4/3/19**
Collaboration with Pfizer on Hem. A gene therapy		*First ever patient dosed with in vivo genome editing therapy (SB-913)*		*Pfizer collaboration expanded to CNS disorders*		*Stock drops due to mixed reactions to early results from SB-913 trial*		*Sangamo and Pfizer release positive data from ALTA study*	

Source: Global Data; Evaluate Pharma; Yahoo Finance; ClearView Analysis. MPS: Mucopolysaccharidosis.

The pipeline focus of non-DNA therapies is relatively similar to that of the industry pipeline, though greater emphasis is placed on genetic disorders.

Top 10 TAs in the Non-DNA Nucleic Acid Therapy Pipeline

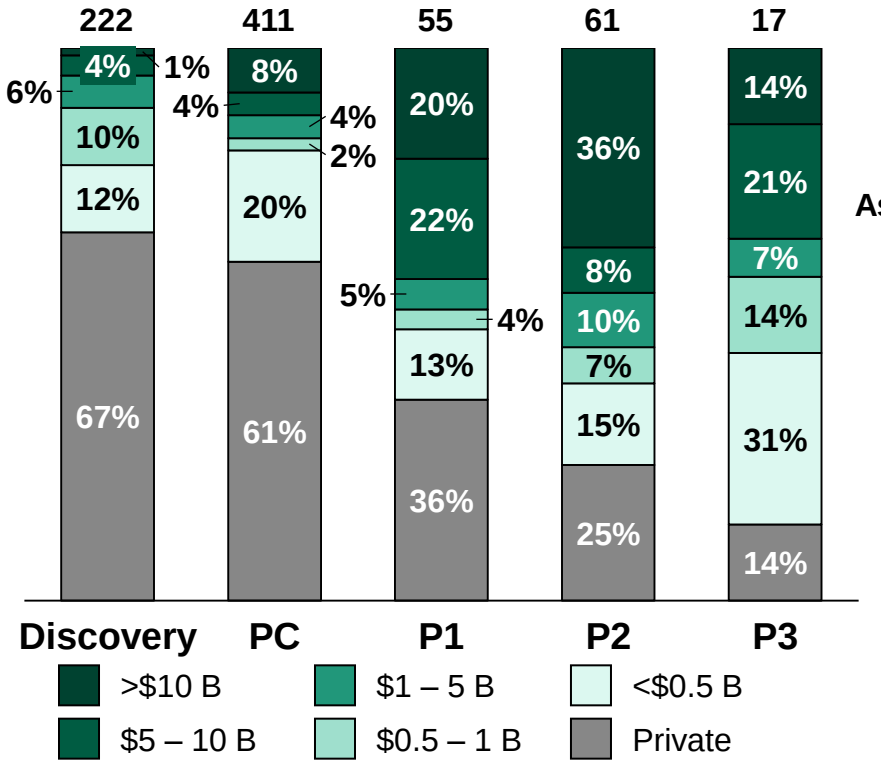


Source: Global Data; Evaluate Pharma; ClearView Analysis. CNS: Central Nervous System; GI: Gastrointestinal. Note: Includes non-global programs captured by Global Data (e.g., development solely in China).

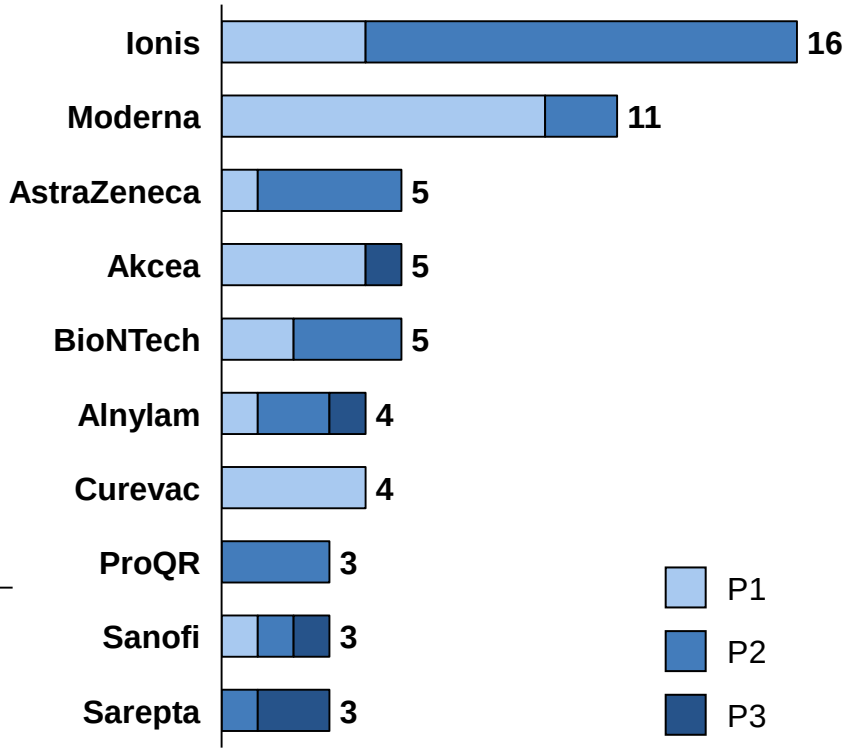
Key players in the late-stage pipeline are comprised of large biotechs that have recently started to commercialize assets (e.g., Ionis, Alnylam, Sarepta).

Top Players in the Non-DNA Nucleic Acid Therapy Pipeline

Distribution of Non-DNA R&D Projects by Market Cap (2019)



Key Players (P1 – 3 Programs, 2019)

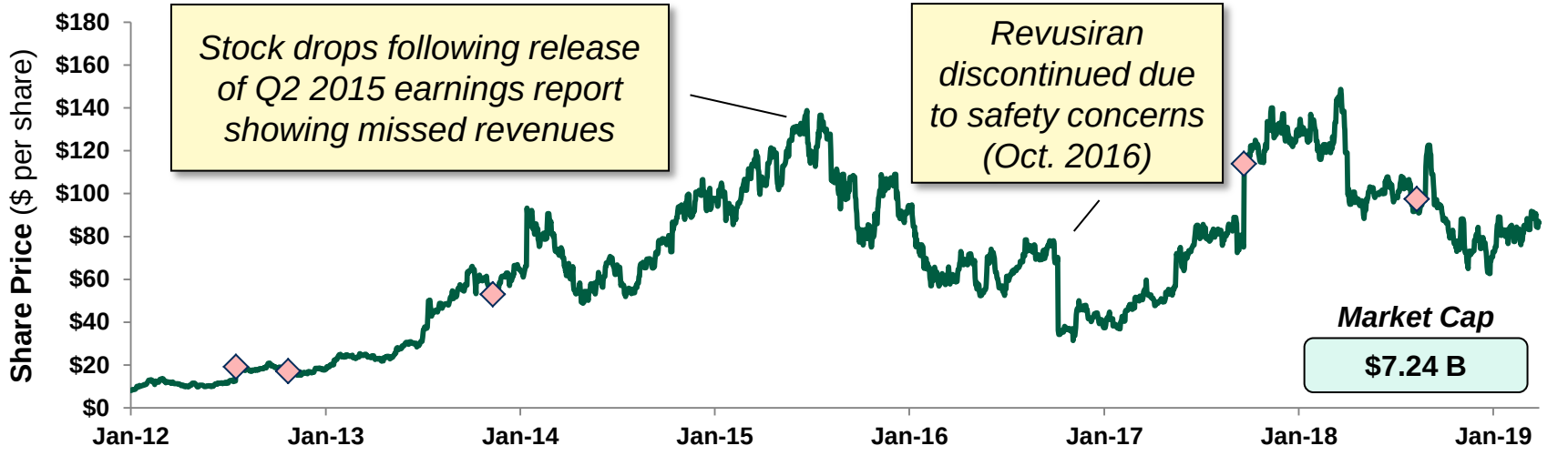


Source: Global Data; Evaluate Pharma; ClearView Analysis. PC: Preclinical. Note: Includes non-global programs captured by Global Data (e.g., development solely in China).

Alnylam has driven its value through a collaboration model for its lead program, with a diverse pipeline of therapies in tow.

Non-DNA Nucleic Acid Development Case Study

Company: Alnylam Pharmaceuticals **Agent:** onpattro (patisiran) lipid complex injection 10 mg/5 mL **Indication:** *Polyneuropathy of hereditary ATTR*



1	7/6/12	2	10/22/12	3	11/10/13	4	9/20/17	5	8/10/18
Positive P1 Trial Results		*Enters into alliance with Genzyme to develop Onpattro*		*Positive P2 trial results*		*Positive topline results from P3 APOLLO study*		*Onpattro approved by FDA as first RNAi therapeutic*	

Source: Global Data; Evaluate Pharma; Yahoo Finance; ClearView Analysis. ATTR: Transthyretin-mediated Amyloidosis.

Trends by Therapeutic Class – Bispecific Antibodies

1 What have been the key trends in pharmaceutical development and innovation in 2018?

2 What therapeutic classes stand out as notable areas for discussion?

Nucleic Acid Technologies

Novel Antibody Technologies

While mAbs have historically been used and studied widely, bispecific antibodies represent a relatively newer class of antibodies.

Key Antibody Technologies in Development

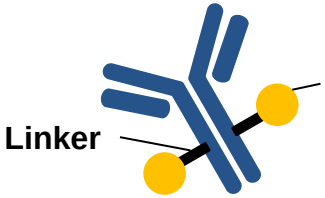
1 Traditional Monoclonal Antibodies

- **Traditional mAbs have been used widely across various therapeutic areas**
- **Concentration within both marketed and pipeline agents is heaviest in oncology and immunology**

Example Agents

Herceptin® trastuzumab — Genentech

HUMIRA® adalimumab — abbvie



2 Antibody Drug Conjugates (ADC)

- **ADCs have been developed to increase potency of antibodies by linking them to cytotoxic agents**
  - The ADC class is still emergent, with few approved agents

Example Agents

ADCETRIS® brentuximab vedotin | for injection — SeattleGenetics®

Kadcyla® trastuzumab emtansine — Roche

3 Bispecific Antibodies

- **Bispecific antibodies are increasingly being explored as novel interventions**
- **Within the oncology space, bispecific antibodies have been deployed to recruit T cells to tumor cells**

Example Agents

HEMLIBRA® emicizumab-kxwh — Roche

BLINCYTO® (blinatumomab) for injection — AMGEN

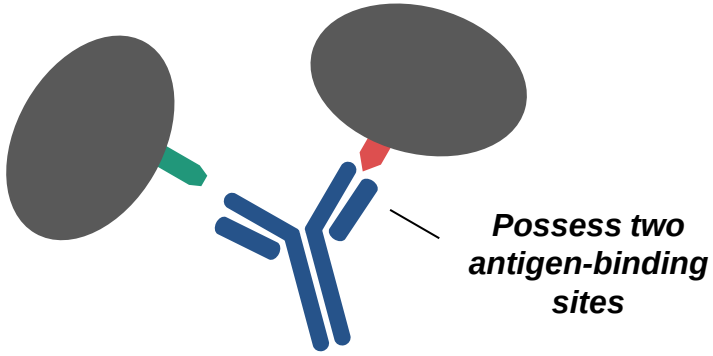
Key: ⬚ Today's Focus

Source: ClearView Analysis. ADC: Antibody Drug Conjugate; TA: Therapeutic Area.

Bispecific antibodies have been approved in oncology and hematology indications, though pipeline activity is primarily concentrated in oncology.

Bispecific Antibody Overview

Description of the Technology



- **Bispecific antibodies in oncology have focused heavily on liquid tumors, aiming to target T cells (e.g., CD3) and cell surface markers (e.g., CD19) on B cells**
- **Though only two bispecifics are approved in the U.S., pipeline activity continues to grow**
- **Bispecific antibodies were prominent at ASH 2018, while early-stage activity has emerged in the immunology space (e.g., RA)**

Approved Agents

BLINCYTO® (blinatumomab) for injection

Manufacturer	*Amgen*
Target	*CD19 x CD3*
Indication[1]	*Refractory B-cell precursor ALL*

HEMLIBRA®

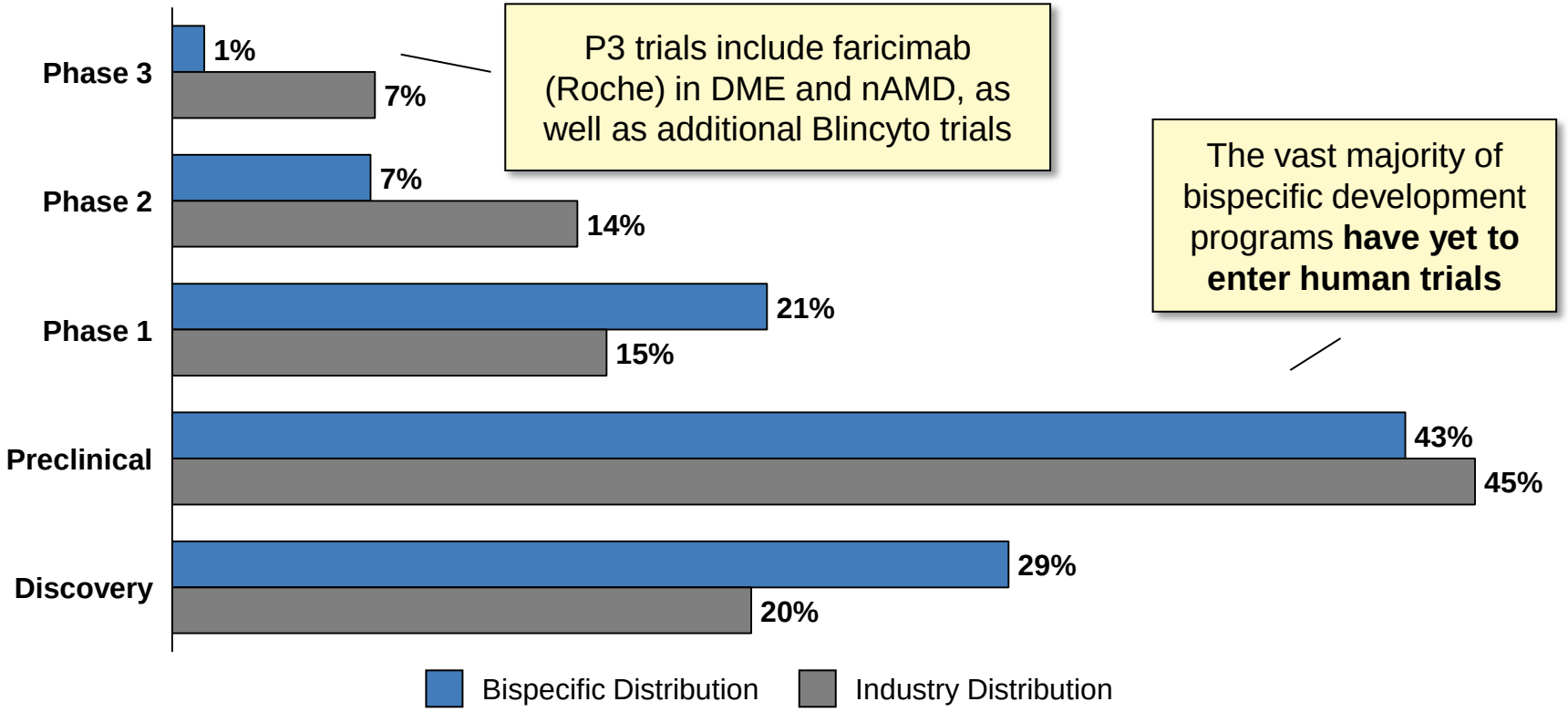
Manufacturer	*Roche*
Target	*Factor IXa x Factor X*
Indication	*Hemophilia A*

Source: ClearView Analysis. ALL: Acute Lymphocytic Leukemia; RA: Rheumatoid Arthritis. [1] Blincyto was also granted accelerated approval to treat B-cell precursor ALL patients who are in remission, bust still have minimal residual disease (MRD).

The bispecific antibody pipeline is relatively nascent compared to the industry pipeline, with few programs in late-stage trials.

Maturity of the Bispecific Antibody Pipeline

Pipeline Distribution by Phase



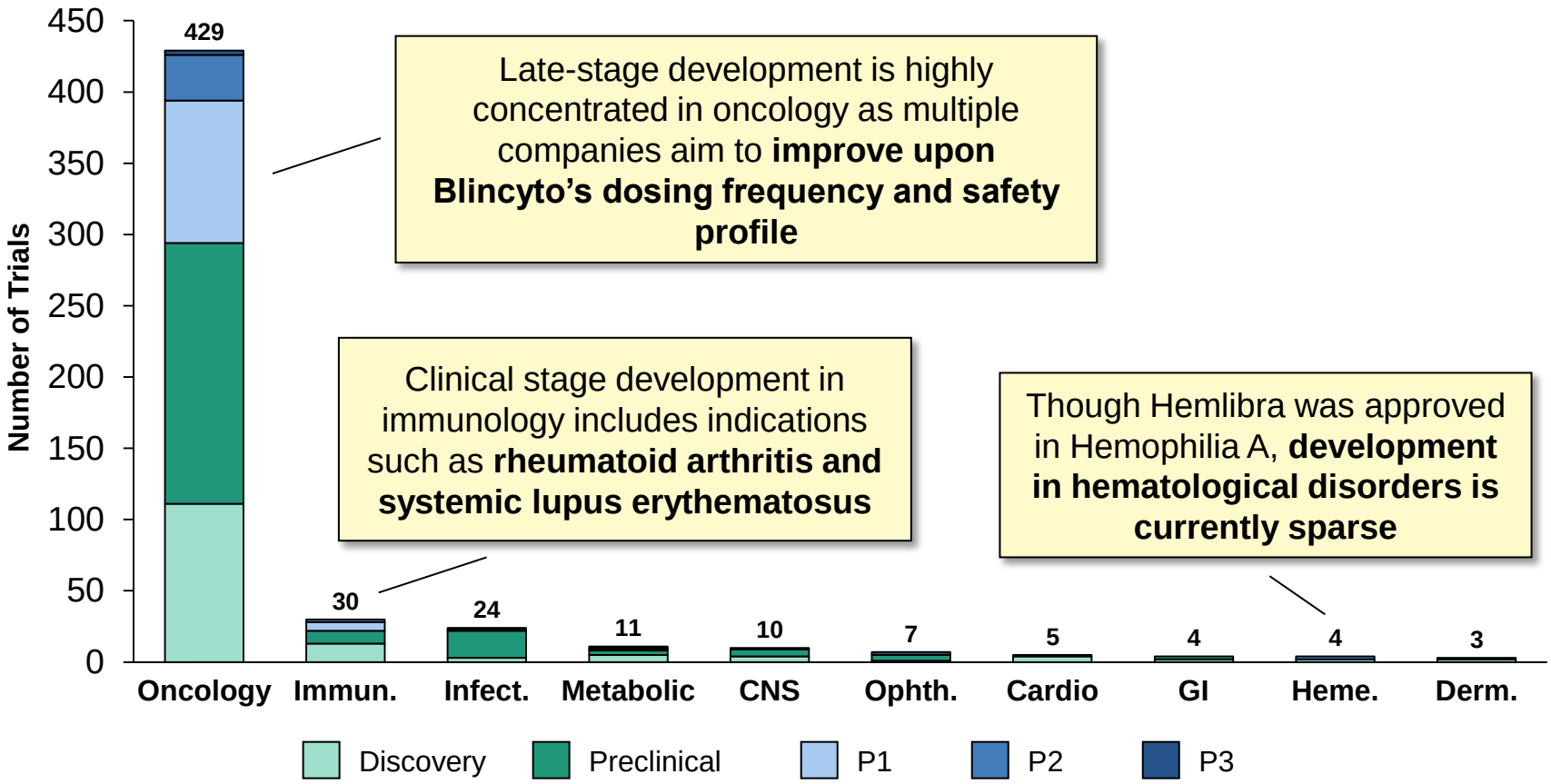
P3 trials include faricimab (Roche) in DME and nAMD, as well as additional Blincyto trials

The vast majority of bispecific development programs **have yet to enter human trials**

Source: Global Data; ClearView Analysis. DME: Diabetic Macular Edema; nAMD: Neovascular (wet) Age-related Macular Degeneration. Note: Includes non-global programs captured by Global Data (e.g., development solely in China).

Bispecific antibody development across all stages is highly concentrated in oncology, with an overwhelming focus on liquid tumors in late-phase trials.

Top 10 TAs in the Bispecific Antibody Pipeline



Late-stage development is highly concentrated in oncology as multiple companies aim to **improve upon Blincyto's dosing frequency and safety profile**

Clinical stage development in immunology includes indications such as **rheumatoid arthritis and systemic lupus erythematosus**

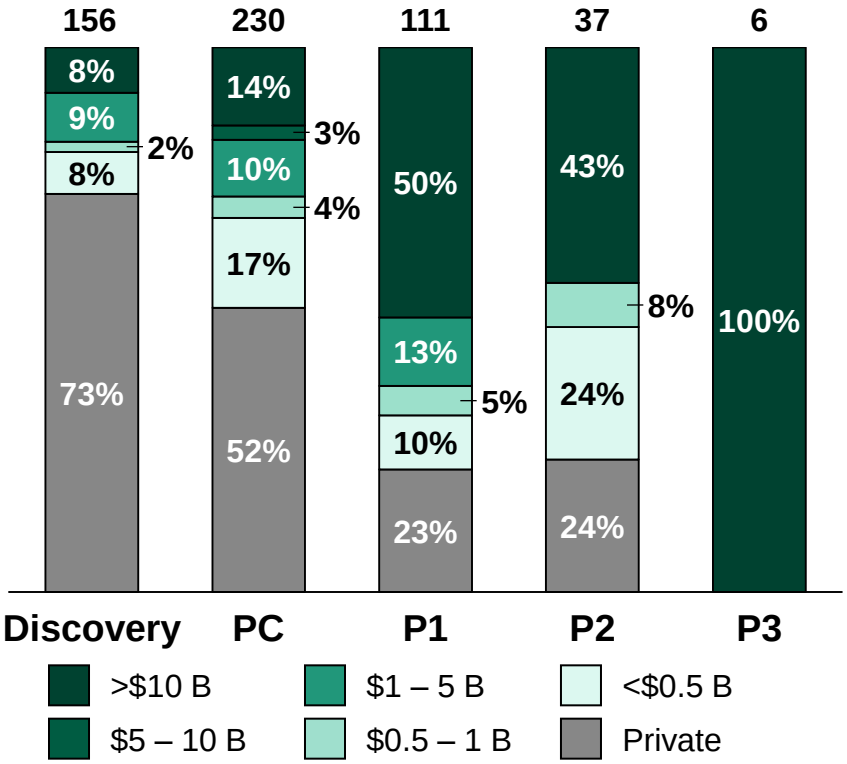
Though Hemlibra was approved in Hemophilia A, **development in hematological disorders is currently sparse**

Source: Global Data; ClearView Analysis. CNS: Central Nervous System; GI: Gastrointestinal. Note: Includes non-global programs captured by Global Data (e.g., development solely in China).

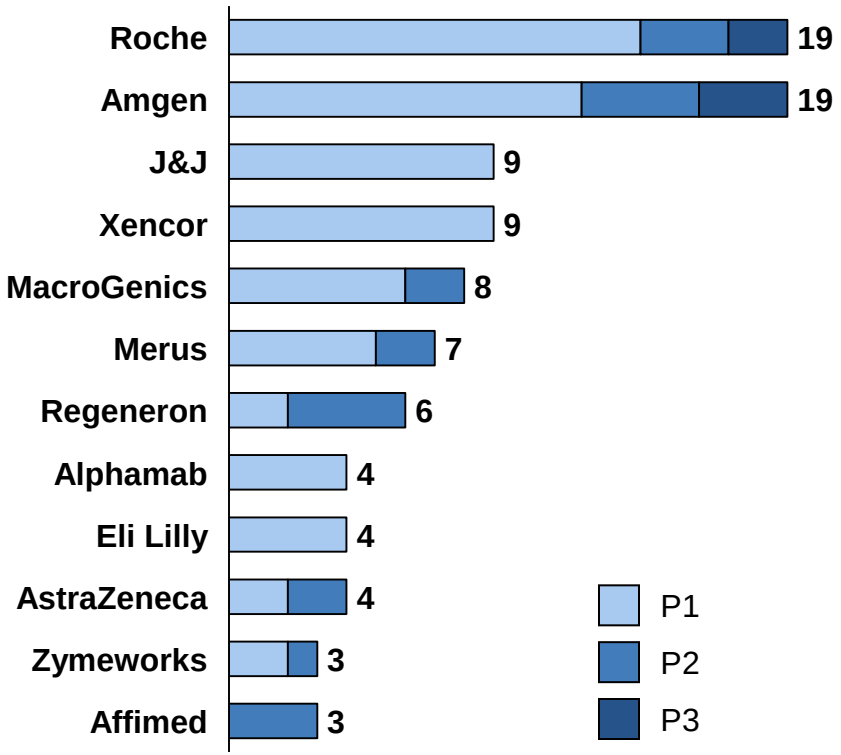
Larger cap companies (>$10 B) dominate the late-stage pipeline, while private companies make up a significant portion of early-stage R&D activity.

Key Players in the Bispecific Antibody Pipeline

Distribution of Bispecific R&D Projects by Market Cap (2019)



Key Players (P1 – 3 Programs, 2019)

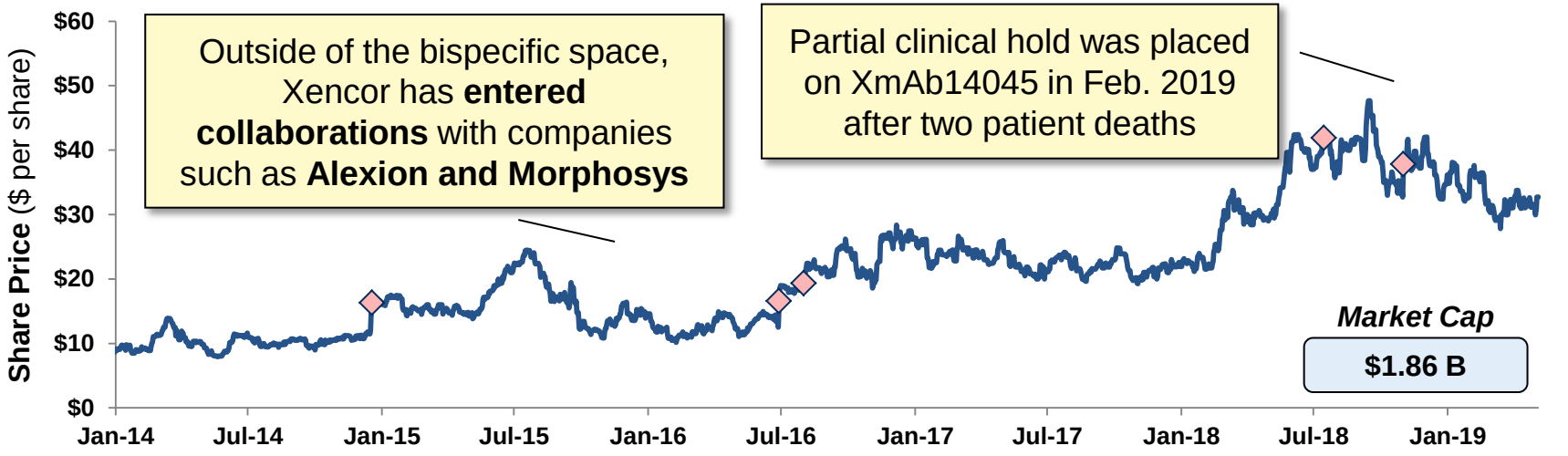


Source: Global Data; ClearView Analysis. PC: Preclinical Note: Includes non-global programs captured by Global Data (e.g., development solely in China).

Xencor has seen a rise in its valuation through parallel development of multiple programs and partnerships.

Bispecific Antibody Development Case Study

Company: xencor **Therapeutic Area(s):** *Immuno-oncology, autoimmune diseases*



1 **12/18/14**	**2** **6/28/16**	**3** **8/1/16**	**4** **7/5/18**	**5** **11/1/18**
Enters discovery collaboration with Novo Nordisk	*Enters Novartis collaboration for XmAb14045 and XmAb13676[1]*	*XmAb14045 initiates P1 trial in R/R AML[2]*	*First patient dosed in P1 XmAb20717 trial in solid tumor patients*	*Positive results announced for XmAb14045 P1 trial*

Source: Global Data; Evaluate Pharma; Yahoo Finance; ClearView Analysis. AML: Acute Myeloid Leukemia; R/R: Relapsed / Refractory. [1] The collaboration with Novartis was recently terminated, citing strategic pipeline reprioritization by Novartis; [2] XmAb14045 trial also includes other CD123-expressing hematologic malignancies.